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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,904	02/09/2000	John B Harley	OMRF 161 CIP	3202

7590 04/23/2003

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	43

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,904	HARLEY ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-10 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the appeal filed on January 14, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Should appellant elect to continue the appeal, the following defects in the appeal must be corrected:

It is noted that the appeal brief states in section (7) that the claims do not stand or fall together and that further explanation is provided. However, there is no further discussion found for which claims stand or fall together in the arguments section.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6-10 and 19-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 35 of copending Application No. 08/781,296 for reasons of record. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the paragraph bridging pages 3-4 of the appeal brief, Applicant states that a terminal disclaimer will be filed upon indication of allowable subject matter.

This rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 6, the "means" clause recited in line 5 of the claim is used in an attempt to recite a claim element for performing a specified function. However, since no function is specified by the word(s) preceding "means," it is impossible to determine the equivalents of the element, as required by 35 U.S.C. 112, sixth paragraph. See *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967). This rejection also affects claims 7-10 because

they are dependent from an indefinite claim and fail to clarify the "means" step recited in claim 6.

Appellant argues that the skilled artisan would be able to determine the scope and meaning of the claim from the teachings in the specification.

Appellant's arguments have been fully considered, but are unpersuasive. The meaning of every term in a claim must be apparent. In the instant case, how the skilled artisan could perform the "means for determining" step is not apparent because the skilled artisan would not know which acts to perform to complete the function recited in the claim. The recited materials used to perform the "means" step are general reagents to detect antibodies, and/or "indicators" of infected cells, Epstein-Barr virus (EBV) DNA or protein. Since the materials recited are general and not specific, the skilled artisan would be unable to ascertain which steps to perform to satisfy the means of determining step in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-10 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting the presence of EBV, does not reasonably provide enablement for predicting the risk of developing lupus by detecting the presence of EBV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 6-10 are drawn to a diagnostic test comprising reagents used to detect the presence of EBV. The active steps recited in claims 19-22 are drawn to a method of obtaining a sample and mixing the sample with reagents used to detect EBV, analyzing the sample and comparing the sample results with control samples.

The nature of the invention

The nature of the invention of claims 6-10 and 19-22 is drawn to a diagnostic test and a method for predicting the likelihood an individual infected with EBV will develop

lupus by comparing control samples from patients not at risk for developing lupus with patient samples. Currently, there is no known predictive indicator to distinguish individuals that will develop lupus from those that will not.

The state of the prior art

Although the prior art recognizes cross-reactivity of some peptides related to EBV and general autoimmune disease, the prior art does not recognize a nexus between the presence of EBV and developing lupus. Normal individuals exposed to EBV have mild symptoms or are asymptomatic, see White et al. page 154, last paragraph and page 343-344.

The abstracts applicant has provided only speculate about the relationship between EBV infection and the development of lupus. The abstracts offer no conclusive data that would indicate that exposure to EBV leads to a greater risk of developing lupus than any other disease. Verdolini et al. discusses only one subject that developed lupus after exposure to EBV and postulates the association between virus and autoimmune disease. This one subject would not indicate that the skilled artisan would recognize EBV as a major risk factor for developing lupus in the general population. Dror et al. states in the first sentence that lupus "...is a multisystem disease of unknown origin...", which supports the conclusions in previous Office actions. The reference also discusses only one subject to illustrate the possible relationship between EBV and lupus. James et al. selected 196 lupus patients and screened them for previous exposure to various viruses. Although almost all of the patients had had prior exposure to EBV compared with the other viruses, it is also noted that the vast majority of "controls", i.e. 95%, also

had been previously exposed to EBV. Therefore, the skilled artisan would be unable to select the appropriate "controls" required by the instant test kit and method because James et al. teach a majority that have been exposed to EBV and do not have lupus. James et al. does not provide data that would indicate factors that a subject would be more likely for developing lupus or any other disease upon EBV exposure. There is no data in the prior art or the specification that would indicate that exposure to EBV is a risk factor for developing lupus or that detecting an antibody to EBV would indicate a predisposition for developing lupus. Marchini et al. (Journal of Autoimmunity. 1994; 7: 179-191) teaches detection of lupus requires the detection of anti-EBNA antibodies as well as autoantibodies specific for SmD, see the abstract and the discussion section. The teachings of Marchini et al. clearly demonstrate that the instant claims are deficient for detecting the risk of developing lupus since more than one factor is required to assay for lupus. With respect to predicting the onset of autoimmune disease, Carson teaches that there are many obstacles for predicting autoimmune disease. Family and population studies indicate that several genes can increase susceptibility of autoimmune disease or influence immune responses to infectious agents that may trigger autoimmunity.

The level of one of ordinary skill

Although it is well within the skill of those in the art to detect the presence of EBV, predicting whether a patient will develop lupus by detecting the presence of EBV is beyond the skill of the ordinary artisan.

The level of predictability in the art

The predictability for determining whether an individual will develop an autoimmune disease, i.e. lupus, is very low. For the level of predictability to be higher, there must be some correlation between exposure to EBV and the development of lupus taught in the prior art or the specification. In this case, there is neither showing. The skilled artisan would be unable to predict, in the absence of proof to the contrary, that the detection of EBV corresponds to the development of lupus. The claim recitations that the instant detection of EBV predicts the likelihood of developing lupus necessarily require evidence to support applicant's assertion.

The amount of direction provided by the inventor

Although data in the specification demonstrates cross-reactivity with specific peptides between EBV and lupus, the assumption that EBV causes or that it is indicative of a possible development of lupus is unsubstantiated. Koch's Postulates correlating lupus with EBV infection has not been satisfied by the prior art or data presented in the disclosure. There has been no evidence that suggests that the test would lead to any determinable outcome or provide any probable conclusion that an individual is more likely to develop lupus.

The existence of working examples

The specification has pointed out cross-reactivities to antibodies derived from EBV and lupus, such as anti-Sm and Epstein-Barr Virus nuclear antigen-1 (EBNA-1), that the applicants have concluded to be the "probable cause of lupus" on page 12, also see example 1. Although the application clearly demonstrates cross-reactivity with

specific peptides between EBV and lupus, the assumption that EBV causes lupus or any other autoimmune disease is inconclusive. There is no evidence presented that clearly indicates lupus is caused by the direct result of exposure to EBV. The specification states that one peptide, SEQ ID 7, is a major epitope found in patients that had mononucleosis, but is not bound by patients with lupus, see page 56. The epitope obviously has the ability to present itself in the immune system indicating that if EBV was present, the epitope would be detected, regardless of what symptoms were presented. Therefore, there must be other unidentified factors that lead to autoimmune disease, making the determination of "likelihood" of development impossible to predict.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Due to the nature of the invention and the claims, which recite predicting a likelihood that an individual will develop lupus upon detection of EBV, the lack of data in the prior art, the disclosure and the working examples indicating a nexus between EBV and the development of lupus, the lack of direction provided that the inventor enabling the skilled artisan a way to select appropriate "controls" that will not develop lupus, the lack of predictability for whether an individual will develop lupus, and the level of skill for being able to predict the onset of disease, it is determined that an undue quantity of

experimentation would be required for one skilled in the art to use the invention in its full scope.

Appellant argues in the appeal brief that the legal requirements have been met because the application discusses a number of examples that differentiate between patients with lupus and controls that do not have lupus. Appellant also argues that the cause-and effect between EBV and lupus must be established is not the legal requirement.

Appellant's arguments have been fully considered, but are found unpersuasive. The specification does not provide a teaching that distinguishes between an EBV-infected individual that will develop lupus and one that will not. Therefore, the recited element in the claims for "predicting the risk of developing lupus" is unsubstantiated. The legal requirement is based on analysis of the discussed factors above, the majority of which have not been satisfied. There must be some evidence provided in the prior art or the specification that there is a correlation between EBV and lupus. The claims are deficient for detecting the risk of developing lupus since the prior art indicates that more than one factor may be a contributor for developing lupus, see the teachings of Carson. Dror et al. (provided by applicant) states in the first sentence that lupus "...is a multisystem disease of unknown origin..." Further, James et al. (also provided by applicant) demonstrates that while almost all 196 lupus patients screened had prior exposure to EBV compared with other viruses, the 95% of the "controls had also been previously exposed to EBV. It is determined that there is no data in the prior art or the specification that would indicate that exposure to EBV is a risk factor for developing lupus or that detecting an antibody to EBV would indicate a predisposition for developing lupus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 7, 10, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Marchini et al. (Journal of Autoimmunity. 1994; 7: 179-191, previously provided in paper no. 37).

The claims are drawn to a diagnostic test and a method to detect levels of antibodies to Epstein-Barr Virus.

Marchini et al. anticipate detecting levels of antibodies to EBV compared to control sera, see the abstract and Table 1 on page 183.

Claims 6, 7, 10, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Petersen et al. (Arthritis and Rheumatism. 1990; 33 (7): 993-1000, previously provided in paper no. 7).

Petersen et al. anticipate detecting levels of antibodies to EBV compared to control sera, see the Materials and Methods section on page 995 and Figure 5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 9, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. supra.

The claims are drawn to peptides consisting of specific sequences. Petersen et al. teach the amino acid sequence corresponding to the EBV nuclear antigen-1 (EBNA-1). Petersen et al. also teach specific peptides derived from EBNA-1 that detect levels of EBV antibodies, see Figure 1 and Table 1 on page 994. Although Petersen et al. do not teach the peptides consisting of the sequences claimed, Petersen et al. teach forming small peptides from the EBNA-1 protein that are cross-reactive with EBV antibodies. The peptides claimed in the instant application are also portions of the EBNA-1 protein and correspond to the peptide sequences taught by Petersen et al. For example, SEQ ID NO: 100 is contained in the E3 peptide taught by Petersen et al. and SEQ ID 38 has matches the C terminal half of E14 and the N terminal half of E11, while SEQ ID NO: 107 overlaps 38 in the E11 portion and ends with the C terminal half of E11. A glycine-alanine rich peptide, P62, was reactive in RA patients and convalescent mononucleosis patients, but had no cross-reactivity with host proteins, see the second paragraph on page 994 and figure 5 on page 997. From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation in producing the claimed invention because of the clear difference in epitope specificity in each group of patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to derive peptides from EBNA-1 to determine which portion of the EBNA protein a patient has specific antibodies to. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify

the peptide derivatives disclosed by Petersen et al. to further identify epitopes distinguishing between different subject populations. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for detecting EBV antibodies to peptides derived from EBNA-1 because Petersen et al. teach that peptides derived from EBNA-1 are cross-reactive with EBV-antibodies. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
April 21, 2003

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